Exhibit 2

CLINICAL ONCOLOGY

Third Edition

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46 Fever in the Neutropenic Cancer Patient

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SUMMARY OF KEY POINTS

INCIDENCE

- Neutropenia is a frequent occurrence in cancer patients due to the underlying disease or its therapy.
- The frequency of infectious complications is related to the degree and duration of neutropenia.
- Infection (either clinically or microbiologically defined) can be documented in about 40% of febrile episodes, and the remaining episodes are of unknown etiology. In either case, empirical antibiotic therapy is essential.

PATHOGENS

- The most common infecting organisms are gram-positive cocci, especially coagulase-negative staphylococci, viridans streptococci, and *Staphylococcus aureus*; the predominant gram-negative pathogens are *Escherichia coli, Klebsiella* spp., and *Pseudomonas aeruginosa.*
- Fungal infections are not uncommon in bone marrow transplant and leukemia patients and are usually caused by *Candida* spp. or *Aspergillus* spp. *Candida albicans* infections are infrequent in the setting of fluconazole® prophylaxis, but non-*C. albicans* are increasing in incidence.

TREATMENT

- Cultures should be collected and antibiotic therapy should be instituted promptly.
- Antibiotic regimen should be active against the common gram-positive cocci and gram-negative bacilli (including *P. aeruginosa*) and may include monotherapy or combinations of antibiotics. However, vancomycin should be strictly reserved for specific indications.
- Low-risk patients (no medical comorbidities) may be treated as outpatients with oral ciprofloxacin plus amoxicillin-clavulanate.
- Predominant pathogens within the hospital and their antibiotic-susceptibility patterns should influence antibiotic selection.
- If the patient has persistent fever after 3 to 4 days, and the infecting organism has not been identified, therapy may be modified if the patient is unstable or new clinical or microbiologic data dictate a change.
- Often it is necessary to institute antifungal therapy on an empirical basis after day 5 to 7 of broad-spectrum antibiotics if the patient is still febrile.
- Treatment of fungal infections is seldom successful unless the neutropenia resolves.
- Colony-stimulating factors and white blood cell transfusions may be considered in some neutropenic patients with a documented infection who are not responding to antimicrobial therapy.

INTRODUCTION

Neutropenia is a common and predictable consequence of many cytotoxic cancer therapies and a frequent complication of malignancies that impair bone marrow function. Neutrophilic granulocytes are a critical component of host defenses, primarily against bacterial and fungal pathogens. They mediate many inflammatory responses toward invading organisms to contain and eliminate infections. Accordingly, a deficit of neutrophils (i.e., neutropenia) is associated with an increase in susceptibility to infections as well as an attenuation of inflammatory responses to infections. Clinical signs and symptoms of inflammation may be muted, even in the setting of active infection in the neutropenic patient. Infection unopposed by innate neutrophil responses can progress rapidly and relentlessly, leading to high levels of morbidity and mortality. Oncologists must be aware of this risk and approach neutropenic cancer patients with care and vigilance.[1]

This chapter focuses on infections during the early phases of chemotherapy-induced neutropenia, primarily in relatively lower risk patients (i.e., those who have solid tumors or who are undergoing autologous stem cell transplant). Patients with acute leukemia or those undergoing allogeneic stem cell transplant are at higher risk for serious infections, and the spectrum of infections in those patients is expanded, as described in Chapter 47.

NEUTROPENIA AS A RISK FACTOR FOR INFECTION

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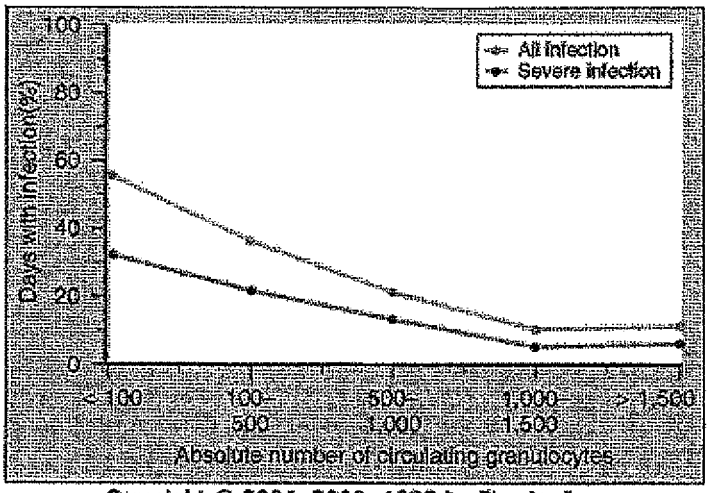
Figure 46-1 Relation between neutrophil count and infection in patients with acute leukemia.

The association between neutropenia and increased infection risk was initially demonstrated by Bodey and colleagues[2] in 1966 in a study of leukemic patients undergoing cytotoxic therapy. The data show that the frequency of infectious complications is inversely related to the degree and duration of neutropenia (Fig. 46-1). Infection risk starts to increase when the neutrophil count decreases to less than 1000 cells/mm^3 and increases dramatically when it is less than 500 cells/mm^3. Fewer than half of the neutropenic patients who become febrile will have an identified or occult infection. In roughly 10% to 20% or more of patients with neutrophil counts less than 100 cells/mm^3, a bloodstream infection will develop. The remainder of patients with fever and neutropenia have a "fever of undetermined origin" (FUO), with no identifiable source despite examination and cultures.[1-3]

The duration of neutropenia also is an important determinant of both infection risk and infection type. Brief durations of neutropenia, particularly those lasting less than 7 days, are associated with a rapid and favorable response to empirical antibiotic therapy.[4] A neutrophil count persistently less than 500 cells/mm^3 for more than 10 days is considered to represent a "high risk" state. Such patients are not only at high risk of developing an infection, but they also are at greater risk for infection-related morbidity and mortality as a consequence of prolonged neutropenia. Prolonged and profound neutropenia is a particular risk for acquiring invasive fungal disease such as *Aspergillus*, a frequently fatal invasive mold infection. The pathogens responsible for initial infections, early in the course of fever and neutropenia, are primarily bacteria and viruses, whereas antibiotic-resistant bacteria, yeast, fungi, and viruses are common causes of subsequent infections. Deaths are usually due to these subsequent infections. Mortality due to initial infections is relatively rare.[5,6]

In addition to cytotoxic chemotherapy, other cases of neutrophil deficiency may be due to bone marrow incompetence as a result of myelodysplastic syndrome or to crowding out of normal granulocytic precursors by tumor cells. "Functional neutropenia" due to impaired neutrophil microbicidal activity may arise as a consequence of underlying disease such as leukemia or therapies such as steroids. Ineffective neutrophil killing leaves the patient highly vulnerable to infection despite seemingly normal peripheral white blood cell counts.



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